ORIGINAL ARTICLE

Safety and Efficacy of Combination 10 Sessions of Q-switched Nd:YAG 1064 nm and Pulsed Dye Laser 595 nm for Melasma Treatment Among Chinese Women in Malaysia.

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Abstract: Melasma is an acquired disorder of facial symmetrical hyperpigmentation due to multiple photomechanical factors. Evidence revealed that treating melasma should be able to target both the hyperpigmentation and the vascular anomalies to overcome the problems related to therapeutic efficacy and safety. The current study aimed to evaluate the safety and effectiveness of combination therapy involving Q-switched Nd: YAG 1064 nm and Pulsed Dye Laser 595 nm in the Chinese population in Malaysia with Fitzpatrick skin phototypes type III to IV. This study involved a retrospective study among 27 Chinese female patients associated with melasma and treated with ten sessions of a combination treatment at three weekly intervals from January 2022 to December 2022. The clinical photographs were examined to assess the mMASI score between the 1st, 5th and 10th treatment's visits. Statistical analysis revealed a significant effect of combination treatment on the mMASI scores reduction across the visits from the 1st visit (8.74±2.95), 5th visit (6.33±2.60), and 10th visit (6.00±3.21). There was a significant difference between the 1st and 5th visit ($p < 0.001$) and between the 1st and 10th visit ($p<0.001$). However, no significant difference was observed between the 5th and 10th visits ($p>0.05$). In terms of treatment's adverse reactions, most patients did not exhibit any adverse reaction (n=19, 70.4%), and only the minority of them demonstrated redness (n=1, 3.7%) and hyperpigmentation (n=7, 25.9%) following the combination treatment. The combination of 10 sessions of Q-switched Nd: YAG 1064 nm and Pulsed Dye Laser 595 nm was proven effective and safe on Chinese female patients with melasma with Fitzpatrick skin phototypes type III to IV.

Keywords: Chinese, Female, Melasma, Pulsed dye laser 595 nm, Q-switched Nd:YAG 1064 nm, Combination treatment, Ten sessions

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Introduction

Melasma is an acquired disorder of symmetrical hyperpigmentation of the face that commonly affects women with Fitzpatrick skin phototypes III to V living in areas of intense ultraviolet (UV) light exposure [1]. In a randomized study involving self-reporting of melasma in a Hispanic female population in 2007, Werlinger et al [2] noted the prevalence to be 8.8%. In Southeast Asia, the prevalence is as high as 40% in females [3]. The Chinese population in Malaysia is also at risk of developing melasma due to their exposure to intense UV rays, similar to other ethnic groups

[4]. Therefore, undoubtedly, melasma would pose an increasingly important skin disorder in the Malaysian population. Furthermore, the pathophysiology of melasma is multifactorial, resulting in treatment resistance and high recurrence rates.

In 2021, Artzi et al [5] conducted a review of 76 relevant articles and identified five main pathomechanisms in melasma: (1) melanocyte inappropriate activation; (2) aggregation of melanin and melanosomes in dermis and epidermis; (3a) increased mast cell count and (3b) solar elastosis; (4) altered basement membrane; and (5) increased vascularization. Additionally, Kim et al [6] suggested that the increased vascularization observed in melasma lesion was due to elevated angiogenic expression of vascular endothelial growth factor (GF) in melasma.

The treatment of melasma ranges from pharmacologic therapy to interventions with chemical peels, laser, and light therapy. Due to the complexity of its pathogenesis, it is even more challenging in skin phototype Fitzpatrick Type III to IV. Despite better photoprotection provided by increased melanin and more dispersed melanosomes in the skin of color, the treatment challenge persists due to photodamage and the risk of post-inflammatory hyperpigmentation (PIH) associated with cutaneous laser therapies. Hence, careful selection of laser devices and treatment parameters is necessary to minimize complications. Ideally, a wide variety of pathomechanisms should be addressed separately with multiple treatment regimens and sessions to maximize results.

Several studies are using different treatment modalities to treat melasma. Most lasers and laser-based combinations have been associated with reduced Melasma Area and Severity Index (MASI), such as the low-fluence Q-switched 1064 nm Nd:YAG laser, fractional ablative CO2 laser, and fractional ablative 2940 nm Er:YAG laser. One significant type of laser most commonly used for treating melasma is the Q-switched Nd:YAG in toning mode, which produces pulses with an extremely high peak of energy delivered in a short time (nanoseconds). This results in the destruction of melanin by a photoacoustic effect. This subcellular selective photothermolysis targets intracellular melanosomes, leading to less inflammation and, consequently, fewer post-inflammatory dyschromia [7]. Therefore, using low-fluence Q-switched Nd:YAG in toning mode with 0.5-1.0 Joules would further reduce the risk of post-inflammatory dyschromia in Fitzpatrick skin phototypes III to IV.

Kim et al [6] have also found that melasma lesions show significant vascularity with increased expression of vascular endothelial growth factor (VEGF), a major angiogenic factor of the skin in altered vasculature of melasma lesions. The systematic review of PubMed, EMBASE, and Cochrane done by Masub et al [8] in 2020 reported five articles (two randomized controlled trials (RCT), one retrospective review, and two case reports) that described the therapeutic effects of pulsed-dye laser (PDL) 595 nm to target the vascular component of melasma. Other than that, a split-face RCT of 17 patients found that PDL with daily triple combination therapy (TCT: hydroquinone, tretinoin, and fluocinolone) was more effective and could prevent melasma relapses than TCT alone [7]. Another retrospective review conducted in 2016 evaluated the efficacy of melasma treatment with PDL and low-power fractional diode laser (1927 nm). The author reported that more than half (54%) of patients showed more than 50% improvement in melasma [9]. Therefore, targeting the angiogenic factor of melasma lesions is crucial, and one approach involves using a 595 nm PDL in combination with the Q-switched Nd:YAG in toning mode.

Pulsed-dye laser is considered a gold-standard laser therapy for cutaneous vascular lesions, and it has been shown to be an effective treatment option when combined with pigment-targeted modalities for melasma patients in several studies [10]. However, only few published papers have been found in the literature utilizing a combination of Q-switched Nd:YAG at 1064 nm

and PDL at 595 nm in individuals with Fitzpatrick skin phototypes III to IV [10-12]. Therefore, a retrospective study was conducted among the Malaysian population receiving melasma treatment using a combination of low-fluence Q-switched Nd:YAG at 1064 nm and PDL at 595 nm. The aim of this study is to assess the safety and effectiveness of a treatment regimen consisting of 10 sessions of combined therapy using Q-switched Nd:YAG at 1064 nm and PDL at 595 nm for treating melasma in Chinese women living in Malaysia. This approach is intended to provide a comprehensive solution addressing the root causes of melasma.

Materials and Method

Study Design and Population

This study is a retrospective study among Chinese patients with melasma treated with a combination treatment of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm between January 2022 and December 2022 at UR KLINIK in Malaysia. Patients were approached to obtain their consent for the treatment and research study. The methods and data collection in this study adhere to ethical standards. The ethics application for the study was obtained from the Hospital UMRA Medical Research Ethics Committee (UMRA-MREC:UMRA MREC003-23). The software G*Power, version 3.1.9.7, was used to determine the sample size with an effect size (partial eta squared: 0.6). Patient's medical records were screened for inclusion and exclusion criteria to identify eligible patients for the study. A thorough screening and review of the patient's medical records and data were conducted to ensure the inclusion and exclusion criteria were met.

The patient's medical records were included if the patient is:

a) Malaysian female of Chinese ethnicity with hyperpigmented skin lesions.
b) Age 40 years old to 60 years old.
c) Fitzpatrick skin phototype III to IV.
d) Undergone 10 sessions of combination low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm treatment within the study period.

The patient's medical records were excluded if:

a) They contained low-quality photographs (e.g. blurry).
b) They were incomplete or missing patient data such as demographics data, photos, parameters data, and consent forms for the treatments.

The electronic patient management systems were used to identify all patients who had undergone combination treatment of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm treatments at UR KLINIK during the study period. The patients underwent a total of 10 sessions with an average interval of four to five weeks between treatments for the combination treatment administered by certified medical aestheticians. The laser settings for the Q-switched Nd:YAG 1064 nm were as follows: 1) Frequency 10Hz, 2) Spot size -8mm, 3) Fluence 0.5-1.0J/cm2. Meanwhile, the laser settings for PDL 595 nm were: 1) Frequency 2 Hz, 2) Spot size -5 mm, 3) Fluence 0.15-0.3 J/cm^2. The patient's medical photographs were examined to assess the improvement in melasma using the modified Melasma Area Severity Index (mMASI) score between the 1st, 5th, and 10th visits. The mMASI score provides a quantitative measurement of the severity of melasma. To minimize potential bias, the mMASI score was assessed by two groups of certified aesthetic doctors with two doctors in each group. The confidentiality of personal data, medical records, and photography was strictly maintained throughout the study.

Measuring Tools

In our study, we have adopted the globally recognized mMASI as the primary assessment tool to evaluate the efficacy of the low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm in

the management of melasma between the 1st, 5th and 10th visits. The mMASI score was used to calculate the severity of the condition based on two factors: the area of involvement and the darkness of the pigmented areas. The mMASI score **(Figure 1)** assesses four areas of the face - forehead, left and right cheeks, and chin whereas the size of the pigmentation is measured on a scale ranging from 0 (no involvement) to 6 (pigmentation covering 90 - 100% of the area). The darkness of the pigmented area was scored visually, ranging from 0 (no pigmentation) to 4 (pigmentation visible). The area and darkness scores for each facial region were multiplied to obtain that region's score, and the total mMASI score was obtained by adding up the scores for all four facial areas. The mMASI score formula was calculated as follows; [0.3A (forehead) x D(forehead) + 0.3A (Left malar) x D (left malar)] + [0.3A (right malar) x D (right malar) + 0.1 x A(chin) x D (chin)]. The total mMASI score ranges from 0 to a maximum of 24, with a higher score indicating more severe melasma. No prior research has documented an investigation into the assessment of treatment efficacy for melasma utilizing the mMASI score in conjunction with a combination of low fluence Q-switched Nd: YAG 1064 nm laser and PDL 595 nm throughout multiple treatment sessions.

The evaluation of the study relied on subjective assessment based on before and after photographs taken from five different angles, as shown in **Figure 2**. All the doctors from the two groups received a two-hour training on the evaluation of facial appearance according to the mMASI score. Each group consists of at least one certified License of Credentialing and Privileging (LCP) doctor. The two groups of doctors evaluated the mMASI score using patients' photographs from the 1st, 5th, and 10th visits, as shown in **Figure 3A, 3B** and **3C**. In situations where there are discrepancies in the mMASI scores, discussions were initiated to facilitate consensus and agreement on the final mMASI score. Any adverse reactions from the start of the treatment until completion were recorded and analyzed.

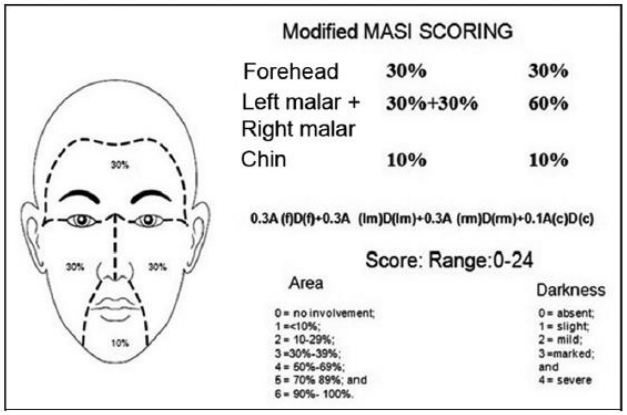
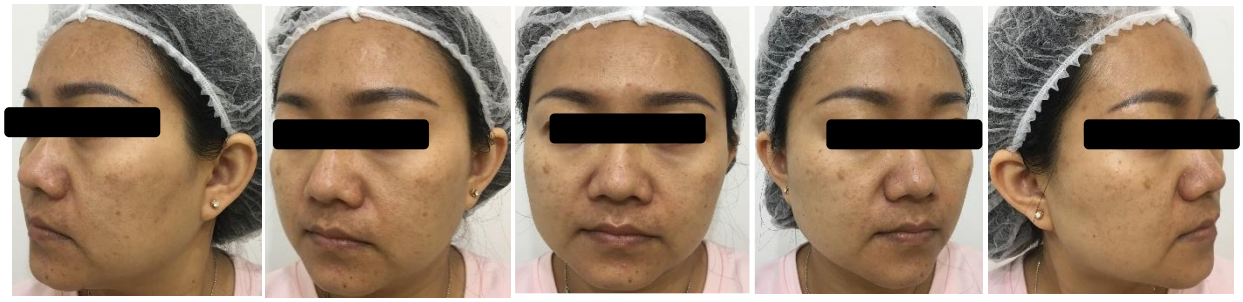


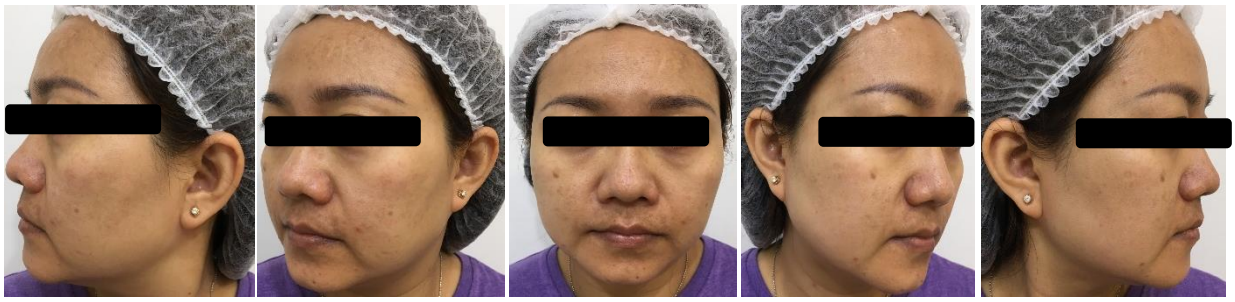
Figure 1 mMASI score [13].

Figure 2 Five different angles photograph [14].

1st visit



5th visit



10th visit

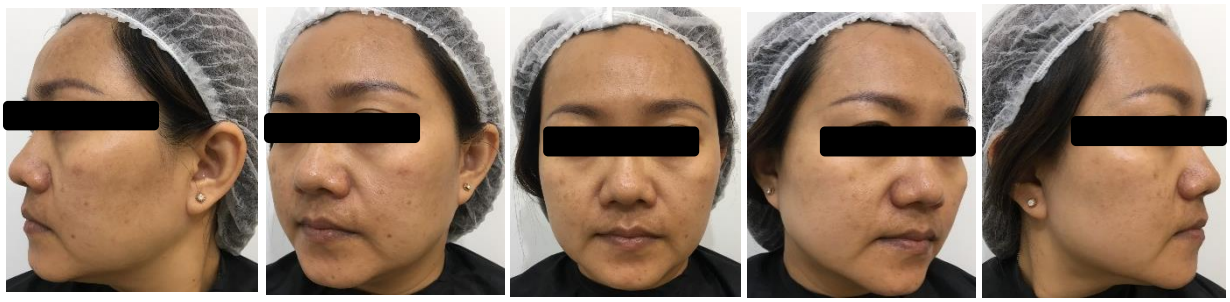
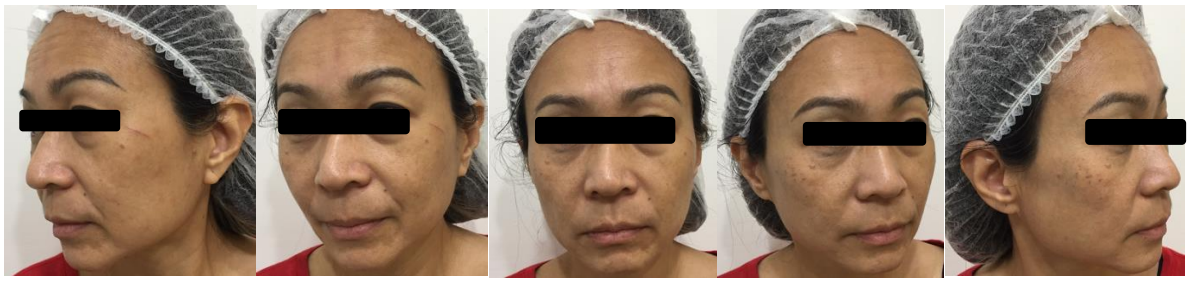
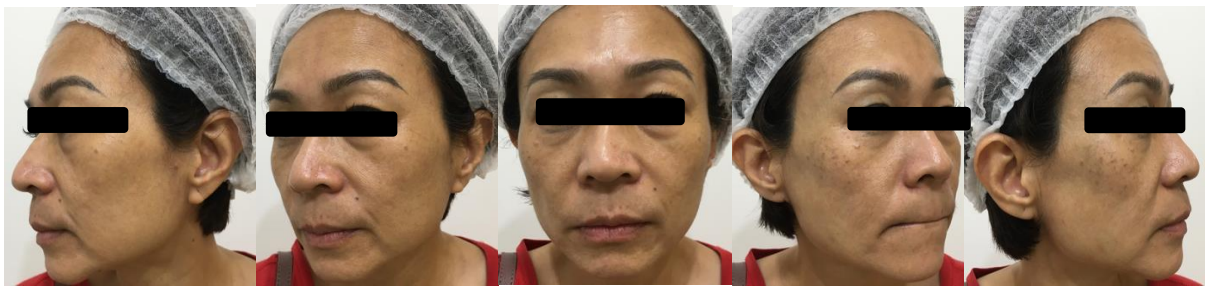


Figure 3A Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

1st visit



5th visit



10th visit

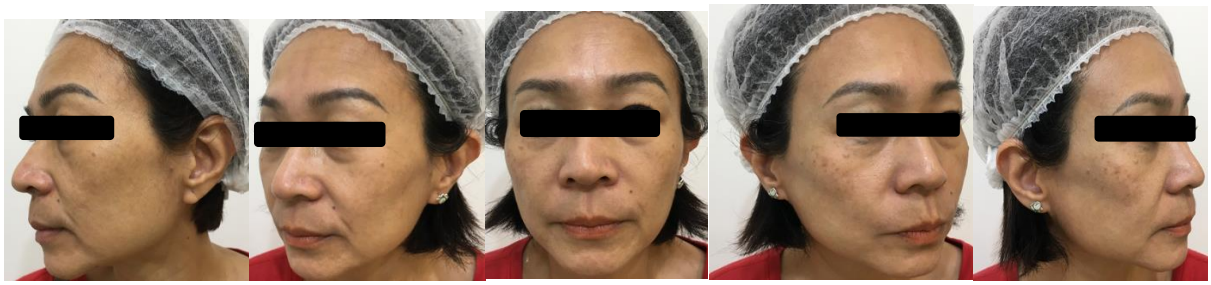
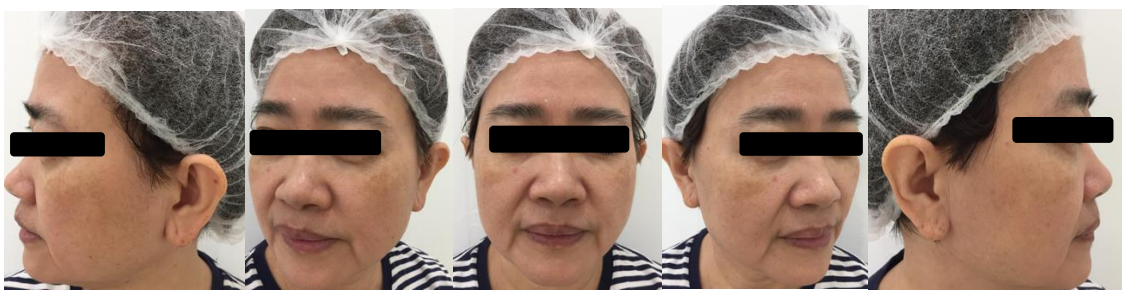
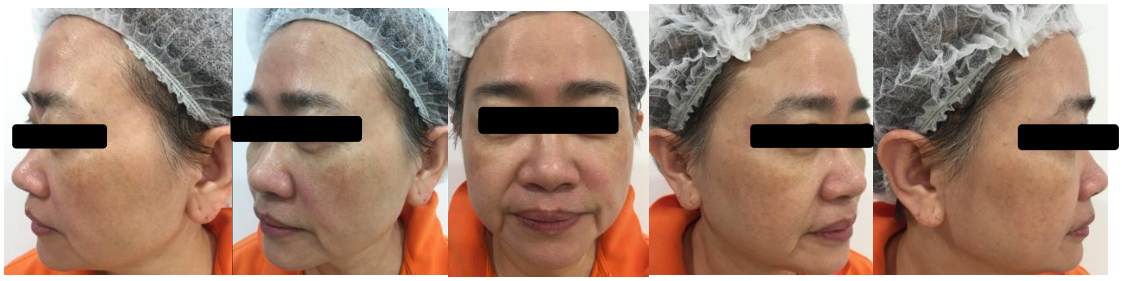


Figure 3B Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

1st visit



5th visit



10th visit

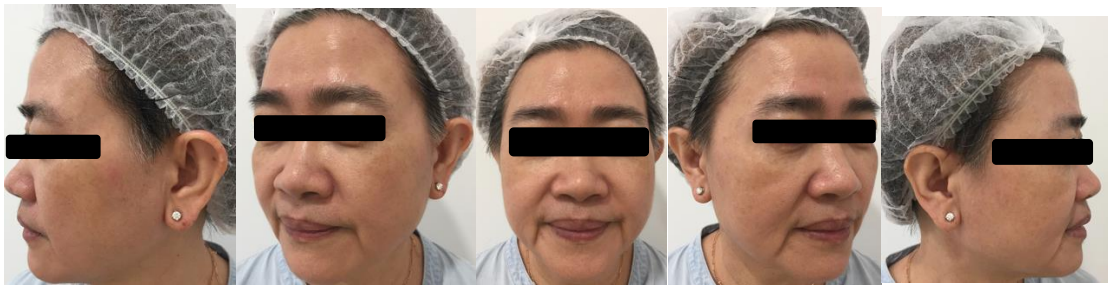


Figure 3C Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 23.0 was applied for descriptive and inferential statistical tests. The descriptive analysis details patients' demographic data, reported as numbers, percentages, mean± standard deviation (SD), where appropriate. A repeated measure Analysis of Variance (ANOVA) was performed to compare and evaluate the treatment outcomes using the mMASI score between the 1st visit, 5th visit, and 10th visit. The significant level will be set at a p-value < 0.05.

Results

A total of 27 patients medical records were included in the study after screening based on the inclusion and exclusion criteria. The current study revealed that the mean age of the patients was 47.70±4.58, while most patients were between 41-45 years old (44.4%). The patients included individuals with Fitzpatrick Skin Type III (n=14, 51.9%) and Fitzpatrick Skin Type IV (n=13, 46.4%). This study noted that the majority of the patients have melasma with freckles (n=11, 48.1%), followed by those who have melasma

with solar lentigines (n=5, 18.5%) and melasma with bilateral nevus of ota like macules (n=2, 7.4%). However, only nine patients (33.3%) have melasma without other hyperpigmentation types. When the treatment's adverse reactions in each visit were evaluated, it was found that the majority of them did not show any adverse reaction (n=19, 70.4%), and the minority of them showed redness (n=1, 3.7%) and hyperpigmentation (n=7, 25.9%) from the combination treatment. For the patient experiencing redness (n=1, 3.7%), 1% hydrocortisone was administered, and the patient was advised to rest for one month before reassessment of the face. Following this intervention, the redness completely resolved. Regarding patients who developed hyperpigmentation (n=7, 25.9%), the majority encountered this issue between the fifth and eighth treatment sessions, coinciding with their perimenopausal age range of 45 to 55 years old. The management strategy for these individuals included counseling of adherence to broad-spectrum sunblock and extending the treatment interval to five to six weeks. As a result, patients observed a reduction in hyperpigmentation. The patient's demographics and clinical profile is summarized in **Table 1**.

Table 1 Patients demographic and clinical profile (n=27).

Variables	n (%)		Mean ± SD
Age (years)			
40-45	12	(44.4)	47.70 ± 4.58
46-50	5	(18.5)	
51-55	9	(33.3)	
56-60	1	(3.7)	
Skin Fitzpatrick Type			
Type III	14	(51.9)	
Type IV	13	(48.2)	
Other Type of Pigmentation			
Bilateral Nevus of Ota-like Macules	2	(7.41)	
Freckles	11	(40.7)	
Solar Lentigines	5	(18.5)	
No other pigmentation	9	(33.3)	
Adverse Reaction			
Redness	1	(3.7)	
Hyperpigmentation	7	(25.9)	
Nil (No adverse effects)	19	(70.4)	

Additionally, using the repeated measure ANOVA, the result showed a statistically significant effect of combination treatment on the mMASI score among patients across the visits, $F(1.62, 42.12) = 22.07$, $p < 0.001$, partial $\eta_p^2 = 0.46$. The current study observed a significant reduction in the mean mMASI score across visits from the 1st visit (8.74±2.95), 5th visit (6.33±2.60), and 10th visit (6.00±3.21). A post hoc pairwise comparison with Bonferroni adjustment indicates a significant difference in the mMASI score between the 1st visit and 5th visit ($p < 0.001$) and between the 1st visit and the 10th visit ($p<0.001$). However, no significant difference was observed between the 5th and 10th visits ($p>0.05$). The mean and SD of the mMASI score across visits are presented in **Table 2**.

Table 2 Mean difference of patients' mMASI score across treatment visits.

Visit Treatment	Mean±SD	Comparison Visit	p-value
1st Visit	8.74 ± 2.95	1st visit - 5th visit	0.000
5th Visit	6.33 ± 2.60	5th visit - 10th visit	0.373
10th Visit	6.00 ± 3.21	1st visit - 10th visit	0.000

Discussion

Hyperpigmented skin lesions are frequently observed among the Chinese population. Among hyperpigmented skin lesions, melasma is a prevalent cutaneous disorder in Southeast Asia, with a prevalence ranging from 0.25% to 4% among individuals seeking medical attention in Dermatology Clinics [15]. Its highest incidence occurs in individuals aged 30 to 44, affecting individuals of all races and genders. It is more commonly observed in women with darker skin types falling within the Fitzpatrick skin types IV to VI. Hence, this study focuses on treating melasma in people with Fitzpatrick skin types III and IV between the ages of 40 and 60, with a higher incidence rate in the female gender.

It is noteworthy that melasma can exert a significant adverse impact on the quality of life of affected individuals, particularly in cases of severe manifestation [16]. Considering the significant societal contributions made by women in our modern context, our research study integrates the utilization of low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm for a safe and efficient treatment of melasma.

Melasma presents a challenge in treatment due to its complexity in the pathology of interactions between the keratinocytes, mast cells, gene regulation abnormalities, neovascularization, and disruption of basement membrane [17]. Various modalities have been employed in the treatment of melasma to target different pathology, and studies have reported that the low fluence Q-switched Nd: YAG is safe for melasma treatment, mainly when using the 1064 nm wavelength in low fluence [18]. However, since neovascularisation is one of the important factors in melasma pathogenesis and low fluence Q-switched Nd:YAG 1064 nm primarily targets melanin, PDL with a wavelength of 595 nm plays a role in treating the vessel abnormalities and has shown promise in treating the vascular component of melasma with a generally favorable safety profile [10]. Pulsed-dye laser targets oxy-hemoglobin in the blood vessels, leading to photothermolysis of the vessels supplying the melasma lesions. Thus, the combination of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm might provide a comprehensive treatment targeting melasma's vascular and pigmented components.

In our study involving a female population from Malaysia, we identified a prevalent occurrence of melasma characterized by a mixed vascularization component. Remarkably, we observed a substantial enhancement in treatment effectiveness as evidenced by a noteworthy decrease in the mean mMASI score from the 1st visit to the 10th visit. This improvement was achieved by implementing a combination approach that effectively addressed melanin accumulation and heightened vascularization. Lee et al. [18] have conducted a comprehensive review of literature on publications from 2009 to 2022 for low fluence Q-switched Nd:YAG 1064 nm laser, including combination treatment, to evaluate the efficacy and adverse events. A systematic PubMed search was conducted, and 42 articles were included in the study. From the study, it was found that low fluence Q-switched Nd:YAG 1064 nm laser appeared to be a generally effective and safe treatment for melasma.

Both low fluence Q-switched Nd:YAG 1064 nm laser and PDL have a risk of post-inflammatory hyperpigmentation (PIH), especially in patients with darker skin types, if not used judiciously. Besides that, some common side

effects include transient erythema (redness) and purpura (purple or red-brown skin discolorations) after a PDL session. Proper patient assessment, treatment protocols, and post -treatment care (sunscreen application and hydration) are vital for safety and achieving the desired outcomes. Nevertheless, it is noteworthy that most patients in our study do not exhibit any adverse reactions to the treatment. Only a few patients developed erythema and hyperpigmentation.

In a previous study, researchers compared two treatments for melasma on a split-face basis: with PDL and 1064 nm Q-switch Nd:YAG laser on one side and only Q-switch Nd:YAG laser on the other. They found that both treatments led to a noticeable reduction in MASI scores on both sides of the face, and there were no significant differences in MASI score changes between the two treatments over the study duration. However, among the patients, seven individuals who had widened capillaries under dermoscopy experienced different MASI score improvements during treatment. It was noted that the use of Q-switched Nd:YAG 1064 nm laser alone on one side resulted in an increase in the MASI score during the follow-up period [10]. This suggest s that the PDL with Q-switched Nd:YAG 1064 nm laser treatment combination is particularly effective when melasma includes visible vascular lesions.

It is believed that VEGF and skin vascularization may play a role in melasma pigmentation [5]. Melanocytes, responsible for skin pigmentation, can respond to angiogenic factors because they have functional VEGF receptors. Vascular endothelial growth factor might directly influence melanocyte behavior through these receptors. Additionally, VEGF stimulates the release of arachidonic acid, which can impact melanin production. By targeting melasma's vascular lesions, PDL might limit melanocyte activation. Our study demonstrated a significant improvement of 27.57% in the mMASI score between the 1st and 5th visits, with a notable 31.45% improvement from the 1st visit to the 10th visit. However, the improvement decreased to 5.32% between the 5th and 10th visits. While we observed statistical significance in the improvement of the mMASI score before and after treatment, the varying outcomes between the 1st to 5th and 5th to 10th visits may be due to the heterogeneous nature of melasma.

Some studies suggest that the selective destruction of melanosomes with minimal damage to melanocytes is a key concept in this treatment, known as ‘subcellular selective photothermolysis’. This technique targets melanosomes, melanocytic dendrites, and subcellular melanin organelles, resulting in significant improvement from the 1st to the 5th visits. However, we hypothesize that the reduced improvement from the 5th to the10th visits may be due to dermal pathology and other factors not directly targeted by laser treatment. Additionally, this treatment not only effectively reduces mMASI scores during the treatment phase but also appears to help prevent relapse after treatment.

Ten sessions of a combinations of Q-switched Nd:YAG 1064 nm laser and PDL 595 nm using low fluence were recommended for the treatment of melasma among Chinese women in Malaysia, as it showed a significant difference in mMASI Score from the 1st to the 10th visits. Despite 25% of patients experiencing hyperpigmentation, a significant portion of them were in their perimenopausal age, during which hormonal fluctuations may occur. Hormones like estrogen and progesterone have been implicated in triggering melasma, with elevated levels correlating with increased skin pigmentation [19]. While complete avoidance of hyperpigmentation may be challenging, counseling on the consistent use of broad-spectrum sunscreen [20] and the addition of other treatment modalities such as polynucleotides [21] and energy-based devices [22] targeting additional photomechanisms of melasma, such as solar elastosis and altered basement membrane, can further help reduce its occurrence.

Limitation

This study is subject to several constraints. Firstly, the sample size employed in this investigation was relatively modest. Consequently, there is a need for future research endeavours to encompass larger sample sizes to yield a more comprehensive assessment of both treatment efficacy and safety. Secondly, the study's participant pool was exclusively composed of individuals from the Chinese ethnicity. Although the recruited Chinese patients exhibited Fitzpatrick skin types III and IV, the absence of patients from other ethnic backgrounds may limit the ability to fully generalize the findings regarding the combined treatment's effectiveness in addressing melasma across diverse ethnic groups. Additionally, the small sample size and reliance on scoring conducted from photographic images rather than clinical evaluation of the actual patients may introduce bias, especially in cases where patients have more than one pigmentary disorder. Future studies could incorporate a control group for comparison to assess the significant difference between the treatment group and the control group. Furthermore, conducting clinical assessments of actual patients followed by scoring based on clinical judgment would help reduce potential biases in the results.

Conclusion

Despite these limitations, this study offered innovative insights into the treatment of melasma. The combination of 10 sessions involving Q-switched Nd:YAG1064 nm and PDL 595 nm has demonstrated effectiveness and safety in treating melasma in individuals with Fitzpatrick skin types III to IV. Although the improvement diminishes between the 5th and 10th visits, the treatment remains safe as the adverse reaction observed is reversable and manageable. Based on our findings, we propose the potential use of additional therapies to target various aspects of melasma either before, during, or after the 5th laser session to optimize results. Further research will be essential to advance our understanding and management of melasma.

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Conflict of Interest

The authors declared no potential conflicts of interest for this article's research, authorship, and/or publication.

References

1. Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. Journal of the American Academy of Dermatology. 2011;65(4):699-714.
2. Werlinger KD, Guevara IL, González CM, Rincón ET, Caetano R, Haley RW, et al. Prevalence of self-diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, Tex. Archives of Dermatology. 2007;143(3):423-31.
3. Sivayathorn A. Melasma in orientals. Clinical Drug Investigation. 1995;10:34-40.
4. Tian WC. Novel technique to treat melasma in Chinese: The combination of 2940-nm fractional Er: YAG and 1064-nm Q-switched Nd: YAG laser. Journal of Cosmetic and Laser Therapy. 2016;18(2):72-4.
5. Artzi O, Horovitz T, Bar-Ilan E, Shehadeh W, Koren A, Zusmanovitch L, et al. The pathogenesis of melasma and implications for treatment. Journal of Cosmetic Dermatology. 2021;20(11):3432-45.

6. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. Journal of Dermatological Science. 2007;46(2):111-6.
7. Cassiano DP, Espósito AC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update on Melasma—part II: treatment. Dermatology and Therapy. 2022;12(9):1989-2012.
8. Masub N, Nguyen JK, Austin E, Jagdeo J. The vascular component of melasma: a systematic review of laboratory, diagnostic, and therapeutic evidence. Dermatologic Surgery. 2020;46(12):1642-50.
9. Geddes ER, Stout AB, Friedman PM. Retrospective analysis of the treatment of melasma lesions exhibiting increased vascularity with the 595-nm pulsed dye laser combined with the 1927-nm fractional low-powered diode laser. Lasers in Surgery and Medicine. 2017;49(1):20-6.
10. Kong SH, Suh HS, Choi YS. Treatment of melasma with pulsed-dye laser and 1,064-nm Q-switched Nd: YAG laser: a split-face study. Annals of Dermatology. 2018;30(1):1-7.
11. Lee YS, Lee YJ, Lee JM, Han TY, Lee JH, Choi JE. The low-fluence Q-switched Nd: YAG laser treatment for melasma: a systematic review. Medicina. 2022;58(7):936.
12. Cassiano DP, Espósito AC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update on melasma—part II: treatment. Dermatology and Therapy. 2022;12(9):1989-2012.
13. Khurana VK, Misri RR, Agarwal S, Thole AV, Kumar S, Anand T. A randomized, open-label, comparative study of oral tranexamic acid and tranexamic acid microinjections in patients with melasma. Indian Journal of Dermatology, Venereology and Leprology. 2019;85:39.
14. Henderson CJ, Larrabee Jr WF, Krieger HB. Photographic standards for facial plastic surgery. Archives of Facial Plastic Surgery. 2005.
15. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. Indian Journal of Dermatology. 2011;56(4):380.
16. Mpofana N, Paulse M, Gqaleni N, Makgobole MU, Pillay P, Hussein A, et al. The Effect of melasma on the quality of life in people with darker skin types living in Durban, South Africa. International Journal of Environmental Research and Public Health. 2023;20(22):7068.
17. Rajanala S, Maymone MB, Vashi NA. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. Dermatology Online Journal. 2019;25(10).
18. Lee YS, Lee YJ, Lee JM, Han TY, Lee JH, Choi JE. The low-fluence Q-switched Nd: YAG laser treatment for melasma: a systematic review. Medicina. 2022;58(7):936.
19. Basit H, Godse KV, Al Aboud AM. Melasma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls; 2023.
20. Fatima S, Braunberger T, Mohammad TF, Kohli I, Hamzavi IH. The role of sunscreen in melasma and post inflammatory hyper-pigmentation. Indian Journal of Dermatology. 2020 ;65(1):5-10.
21. Cavallini M, Bartoletti E, Maioli L, Massirone A, Pia Palmieri I, Papagni M, et al. Consensus report on the use of PN-HPT™(polynucleotides highly purified technology) in aesthetic medicine. Journal of Cosmetic Dermatology. 2021;20(3):922-928.
22. Reynal S, Martin E, Munavalli G. Energy-based devices for melasma and post inflammatory hyperpigmentation. Dermatological Reviews. 2023;4(1):58-66.